THE LANCET
Infectious Diseases

## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Hansen CH, Friis NU, Bager P, et al. Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a nation-wide population-based study in Denmark. *Lancet Infect Dis* 2022; published online Oct 18. https://doi.org/10.1016/S1473-3099(22)00595-3.

# Risk of reinfection, vaccine protection, and severity of infection with the BA.5 omicron subvariant: a Danish nation-wide population-based study

**SUPPLEMENTARY MATERIAL**

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# Contents

## ADDITIONAL DESCRIPTION OF METHODS

In accompaniment of the methods section additional information is provided below on the national test strategy, vaccination programme and genomic sequencing methods.

### National test strategy

Unless older than 65 years of age or otherwise more vulnerable to COVID-19, such as during pregnancy or if immunocompromised for other reasons, or if testing may inform treatment options, regular PCR testing is no longer strongly recommended or mandated, even if suspecting COVID-19. This does not mean, however, that PCR testing in the remaining population is unavailable or advised against as many test centres across the country have remained open continuing to offer free-of-charge PCR testing to all citizens. As described elsewhere (Bager *et al*., 2022), the test system is divided into a community track with test centres open to citizens and samples analysed at one laboratory site (TestCenter Denmark, TCDK), and a health care track with regional testing at clinics and hospitals and samples processed at 10 hospital laboratories (Departments of Clinical Microbiology).

### Vaccination programme

Starting 27 December 2020, vaccinations were offered with priority given to the elderly, those in the healthcare professions or otherwise most at risk of infection or severe disease. By August 2021, all over the age of 12 years had been offered a primary vaccination series. In the autumn of 2021, a booster dose was offered to selected priority groups before being offered more widely from December 2021 to all adults (18+ year-olds) who had completed their primary vaccination series more than 4.5 months earlier. (A small number of elderly and at-risk individuals received a second booster dose in the first half of 2022.) The majority received a primary vaccination series consisting of two mRNA doses with either Cominarty (Pfizer-BioNTech; BNT162b2) (~84%) or Spikevac (Moderna; mRNA-1273; ~12%), while a minority received the adenovector vaccines Vaxzevria (Oxford-AstraZeneca; ChAdOx1; ~3%), or Johnson & Johnson (Ad26.COV2.S JNJ-78436735; VAC31518; ~1%). (Bager *et al*., 2022.)

### Genomic sequencing methods

Briefly, at the SSI the WGS was performed using the ARTIC v3 amplicon sequencing panel (https://artic.network) with slight modifications including primer spike-ins. Samples were sequenced on either the NextSeq or NovaSeq platforms (Illumina) where consensus sequences were called using an in-house implementation of IVAR with a custom BCFtools command for consensus calling. From the regional laboratories, consensus sequences were obtained. Subvariants on all genomes were called on the generated consensus sequences containing less than 3,000 missing sites or ambiguous sites using Pangolin with the PangoLEARN assignment algorithm.

**CHARACTERISTICS OF THE COMPARISON GROUPS IN ANALYSIS 1, 2 AND 3**

**Table s1** Comparison of cases and controls from Analysis 1.

| | Cases | | Controls | |
|---|---|---|---|---|
| | *Number* | *%* | *Number* | *%* |
| **Total** | 8,678 | 100 | 178,669 | 100 |
| | | | | |
| **Female** | 4,363 | 50.3 | 96,029 | 53,7 |
| **Male** | 4,315 | 49.7 | 82,640 | 46,3 |
| **Age (years)** | | | | |
| 18-24 | 381 | 4.4 | 9,881 | 5.5 |
| 25-34 | 861 | 9.9 | 16,205 | 9.1 |
| 35-44 | 820 | 9.5 | 17,415 | 9.8 |
| 45-54 | 1,720 | 19.8 | 28,051 | 15.7 |
| 55-64 | 2,120 | 24.4 | 35,426 | 19.8 |
| 65-74 | 1,752 | 20.2 | 33,359 | 18.7 |
| 75-84 | 866 | 10.0 | 27,040 | 15.1 |
| 85+ | 158 | 1.8 | 11,292 | 6.3 |
| **Region of residency** | | | | |
| Capital | 2,893 | 33.3 | 60,426 | 33.8 |
| Central Denmark | 2,012 | 23.2 | 35,545 | 19.9 |
| Northern Denmark | 764 | 8.8 | 15,768 | 8.8 |
| Zealand | 1,235 | 14.2 | 28,714 | 16.0 |
| Southern Denmark | 1,774 | 20.4 | 38,216 | 21.4 |
| **Number of comorbidities*** | | | | |
| None | 6,679 | 77.0 | 121,450 | 68.0 |
| One | 1,479 | 17.0 | 37,779 | 21.1 |
| Two | 394 | 4.5 | 13,802 | 7.7 |
| Three or more | 126 | 1.5 | 5,638 | 3.2 |
| **COVID-19 vaccinations$** | | | | |
| Unvaccinated | | | | |
| Only primary vaccination completed – 2 mRNA doses | | | | |
| Only primary vaccination completed – non-mRNA | | | | |
| Primary (mRNA) vaccination + 1 (mRNA) booster dose | 8,678 | 100 | 178,669 | 100 |
| Primary (non-mRNA) vaccination + 1 (mRNA) booster dose | | | | |
| Primary vaccination + 2 booster doses (any type) | | | | |
| Other¤ | | | | |
| **PCR-confirmed SARS-CoV-2 infections‡** | | | | |
| No previous infection | 8,468 | 97.6 | 144,697 | 81.0 |
| At least 1 previous infection | 210 | 2.4 | 33,972 | 19.0 |
| Infection likely with omicron | 210 | 100 | 33,972 | 100 |
| Infection likely with earlier variant | 0 | 0 | 0 | 0 |

$ Vaccinations received by April 10, 2022: mRNA vaccines were either BNT162b2 or mRNA-1273, non-mRNA vaccines included JCOVDEN and ChAdOx1-S. ¤Incomplete primary vaccination or non-mRNA booster doses. *Comorbidities registered in the past 5 years out of the following: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune deficiency conditions. ‡ Infection status by April 10, 2022.

**Table s2** Comparison of vaccinated and unvaccinated from Analysis 2.

| | 3x mRNA vaccinated | | Unvaccinated | |
|---|---|---|---|---|
| | *Number* | *%* | *Number* | *%* |
| **Total** | 39,888 | 100 | 2,262 | 100 |
| | | | | |
| **Female** | 20,686 | 51.9 | 1,248 | 55.2 |
| **Male** | 19,202 | 48.1 | 1,014 | 44.8 |
| **Age (years)** | | | | |
| 18-24 | 1,572 | 3.9 | 255 | 11.3 |
| 25-34 | 3,316 | 8.3 | 653 | 28.9 |
| 35-44 | 3,632 | 9.1 | 418 | 18.5 |
| 45-54 | 7,588 | 19.0 | 413 | 18.3 |
| 55-64 | 9,451 | 23.7 | 304 | 13.4 |
| 65-74 | 8,356 | 21.0 | 132 | 5.8 |
| 75-84 | 4,886 | 12.3 | 58 | 2.6 |
| 85+ | 1,087 | 2.7 | 29 | 1.3 |
| **Region of residency** | | | | |
| Capital | 11.746 | 29.5 | 823 | 36.4 |
| Central Denmark | 9.425 | 23.6 | 449 | 19.9 |
| Northern Denmark | 4.355 | 10.9 | 194 | 8.6 |
| Zealand | 5.753 | 14.4 | 336 | 14.9 |
| Southern Denmark | 8.609 | 21.6 | 460 | 20.3 |
| **Number of comorbidities*** | | | | |
| None | 29,781 | 76.7 | 1,911 | 84.5 |
| One | 7,359 | 18.5 | 276 | 12.2 |
| Two | 2,066 | 5.2 | 58 | 2.6 |
| Three or more | 682 | 1.7 | 17 | 0.8 |
| **COVID-19 vaccinations$** | | | | |
| Unvaccinated | | | 2,262 | 100 |
| Only primary vaccination completed – 2 mRNA doses | | | | |
| Only primary vaccination completed – non-mRNA | | | | |
| Primary (mRNA) vaccination + 1 (mRNA) booster dose | 39,888 | 100 | | |
| Primary (non-mRNA) vaccination + 1 (mRNA) booster dose | | | | |
| Primary vaccination + 2 booster doses (any type) | | | | |
| Other¤ | | | | |
| **PCR-confirmed SARS-CoV-2 infections‡** | | | | |
| No previous infection | 37,568 | 94.2 | 1,639 | 72.5 |
| At least 1 previous infection | 2,320 | 5.8 | 623 | 27.5 |
| Infection likely with omicron | 1,069 | 46.1 | 291 | 46.7 |
| Infection likely with earlier variant | 1,251 | 53.9 | 332 | 53.3 |

$ Vaccinations received by April 10, 2022: mRNA vaccines were either BNT162b2 or mRNA-1273, non-mRNA vaccines included JCOVDEN and ChAdOx1-S. ¤Incomplete primary vaccination or non-mRNA booster doses. *Comorbidities registered in the past 5 years out of the following: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune deficiency conditions. ‡ Infection status by April 10, 2022.

**Table s3** Comparison of BA.5 and BA.2 cases from Analysis 3.

| | BA.5 cases | | BA.2 cases | |
|---|---|---|---|---|
| | *Number* | *%* | *Number* | *%* |
| **Total** | 11,314 | 100 | 36,805 | 100 |
| | | | | |
| **Female** | 5,875 | 51.9 | 19,740 | 53.6 |
| **Male** | 5,439 | 48.1 | 17,065 | 46.4 |
| **Age (years)** | | | | |
| 18-24 | 5,89 | 5.2 | 1,638 | 4.5 |
| 25-34 | 1,503 | 13.3 | 4,000 | 10.9 |
| 35-44 | 1,314 | 11.6 | 3,753 | 10.2 |
| 45-54 | 2,296 | 20.3 | 6,842 | 18.6 |
| 55-64 | 2,596 | 23.0 | 8,376 | 22.8 |
| 65-74 | 1,914 | 16.9 | 6,966 | 18.9 |
| 75-84 | 934 | 8.3 | 4,228 | 11.5 |
| 85+ | 168 | 1.5 | 1,002 | 2.7 |
| **Region of residency** | | | | |
| Capital | 3,998 | 35.3 | 10,521 | 28.6 |
| Central Denmark | 2,568 | 22.7 | 8,649 | 23.5 |
| Northern Denmark | 970 | 8.6 | 4,234 | 11.5 |
| Zealand | 1,550 | 13.7 | 5,385 | 14.6 |
| Southern Denmark | 2,228 | 19.7 | 8,016 | 21.8 |
| **Number of comorbidities*** | | | | |
| None | 8,796 | 77.7 | 27,428 | 74.5 |
| One | 1,869 | 16.5 | 6,713 | 18.2 |
| Two | 478 | 4.2 | 1,946 | 5.3 |
| Three or more | 171 | 1.5 | 718 | 2.0 |
| **COVID-19 vaccinations$** | | | | |
| Unvaccinated | 571 | 5.1 | 1,702 | 4.6 |
| Only primary vaccination completed – 2 mRNA doses | 40 | 0.4 | 61 | 0.2 |
| Only primary vaccination completed – non-mRNA | 6 | 0.1 | 21 | 0.1 |
| Primary (mRNA) vaccination + 1 (mRNA) booster dose | 9,323 | 82.4 | 30,625 | 83.2 |
| Primary (non-mRNA) vaccination + 1 (mRNA) booster dose | 476 | 4.2 | 1,610 | 4.4 |
| Primary vaccination + 2 booster doses (any type) | 133 | 1.2 | 530 | 1.4 |
| Other¤ | 765 | 6.8 | 2,256 | 6.1 |
| **PCR-confirmed SARS-CoV-2 infections‡** | | | | |
| No previous infection | 9,849 | 87.1 | 34,438 | 93.6 |
| At least 1 previous infection | 1,465 | 13.0 | 2,367 | 6.4 |
| Infection likely with omicron | 701 | 47.9 | 1,013 | 42.8 |
| Infection likely with earlier variant | 764 | 52.2 | 1,354 | 57.2 |

$ Vaccinations received by April 10, 2022: mRNA vaccines were either BNT162b2 or mRNA-1273, non-mRNA vaccines included JCOVDEN and ChAdOx1-S. ¤Incomplete primary vaccination or non-mRNA booster doses. *Comorbidities registered in the past 5 years out of the following: diabetes, adiposity, haematological and other cancers, neurological diseases, kidney diseases cardiovascular diseases, chronic pulmonary diseases, respiratory diseases, and immune deficiency conditions. ‡ Infection status by April 10, 2022.

**PROTECTION AGAINST REINFECTION LEADING TO HOSPITALISATION: SUPPLEMENTARY ANALYSIS**

**Table s4** Protection after a prior positive SARS-CoV-2 PCR test against hospitalisation due to a BA.5 or BA.2 infection, April to June, 2022, Denmark.

| | Hospitalised for COVID-19 | Controls | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Estimated protection, % (95% CI) |
|---|---|---|---|---|---|
| **BA.5 cases** | | | | | **protection against BA.5** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 1 ( 0.6) | 33,972 (19.0) | 0.025 (0.003; 0.177) | 0.036 (0.005; 0.258) | 96.4 (74.2; 99.5) |
| **Unexposed** | 172 (99.4) | 144,697 (81.0) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 0 ( 0.0) | 3,336 ( 2.3) | | | |
| **Unexposed** | 172 (100) | 144,697 (97.7) | | | |
| | | | Not enough cases to reliably estimate protection | | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 0 ( 0.0) | 1,878 ( 1.3) | | | |
| **Unexposed** | 172 (100) | 144,697 (98.7) | | | |
| **BA.2 cases** | | | | | **protection against BA.2** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 4 ( 1.0) | 33,972 (19.0) | 0.044 (0.016; 0.118) | 0.088 (0.033; 0.237) | 91.2 (76.3; 96.7) |
| **Unexposed** | 387 (99.0) | 144,697 (81.0) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 1 ( 0.3) | 3,336 ( 2.3) | | | |
| **Unexposed** | 387 (99.7) | 144,697 (97.7) | | | |
| | | | Not enough cases to reliably estimate protection | | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 0 ( 0.0) | 1,878 ( 1.3) | | | |
| **Unexposed** | 387 (100) | 144,697 (98.7) | | | |

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 30, 2022 and admitted to hospital with a COVID-19 primary diagnosis code; controls tested negative during the same period. OR denotes odds ratio; CI denotes confidence interval. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for age group, time (week number), sex, region and comorbidity.

**PROTECTION AGAINST REINFECTION: SENSITIVITY ANALYSIS 1**

To assess the robustness of the findings under an alternative analysis approach, Analysis 1 was repeated using a matched case-control design in which cases and controls were pair-matched on test date, sex and age. Specifically, for each BA.5 case identified during the outcome period, a control person of the same age and sex was selected at random among those who tested negative on the same day (and who had not previously tested positive during the outcome period). The case was dropped from the analysis if no match was found. The matched pairs were then analysed in an exact conditional logistic regression model with adjustment for area of residency and comorbidity as for the main analysis.

**Table s5** Sensitivity analysis using a matched case-control design: Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, April to June, 2022, Denmark.

| | Cases | Matched controls | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Estimated protection, % (95% CI) |
|---|---|---|---|---|---|
| | **BA.5 cases** | | | | **protection against BA.5** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 210 ( 2.4) | 2,063 (23.9) | 0.071 (0.060; 0.084) | 0.071 (0.059; 0.084) | 92.9 (91.6; 94.1) |
| **Unexposed** | 8,409 (97.6) | 6,556 (76.1) | 1 | 1 | |
| *Exposure: prior delta infection ‡* | | | | | |
| **Exposed** | 65 ( 0.8) | 255 ( 3.0) | 0.243 (0.184; 0.321) | 0.247 (0.186; 0.327) | 75.3 (67.3; 81.4) |
| **Unexposed** | 8,328 (99.2) | 8,138 (97.0) | 1 | 1 | |
| *Exposure: prior alpha infection ‡* | | | | | |
| **Exposed** | 57 ( 0.7) | 136 ( 1.6) | 0.415 (0.304; 0.566) | 0.420 (0.307; 0.575) | 58.0 (42.5; 69.3) |
| **Unexposed** | 8,314 (99.3) | 8,235 (98.4) | 1 | 1 | |
| | **BA.2 cases** | | | | **protection against BA.2** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 192 ( 0.7) | 5,094 (17.4) | 0.029 (0.025; 0.034) | 0.030 (0.025; 0.035) | 97.0 (96.5; 97.5) |
| **Unexposed** | 29,044 (99.3) | 24,142 (82.6) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 100 ( 0.3) | 683 ( 2.4) | 0.144 (0.116; 0.178) | 0.152 (0.123; 0.188) | 84.8 (81.2; 87.7) |
| **Unexposed** | 28,941 (99.7) | 28,358 (97.6) | 1 | | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 97 ( 0.3) | 370 ( 1.3) | 0.254 (0.202; 0.319) | 0.267 (0.212; 0.336) | 73.3 (66.4; 78.8) |
| **Unexposed** | 28,925 (99.7) | 28,652 (98.7) | 1 | 1 | |

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 30, 2022; controls tested negative during the same period. Cases and controls were pair-matched on test date, sex and age. A matched control was identified for over 99% (or over 98% if indicated with ‡) of all relevant cases identified during the outcome period. OR denotes odds ratio; CI denotes confidence interval. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for region and comorbidity in an exact conditional logistic regression taking account of the pair-matching.

**PROTECTION AGAINST REINFECTION: SENSITIVITY ANALYSIS 2**

In the main analysis, the exposure period end date was 60 days before the start of the outcome period to ensure at least that number of days between a previous infection and a potential new infection during the outcome period as the analysis did not rely on genome sequenced samples from the exposure period. Results of two sensitivity analyses are presented in the below two tables. In the first analysis (table s6) a minimum of 90 days is required between the first and second positive tests in order for the second test to be included as a reinfection. In the second analysis (table s7) no such delay is required meaning that a case with a previous positive test at any point in 2022 prior to the outcome period will be counted as a reinfection. Further details of the methods used are provided in the footnotes accompanying the tables.

**Table s6** Sensitivity analysis with reinfection requiring a new positive PCR test being at least 90+ days after the primary infection: Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, May to June, 2022, Denmark.

| | Cases | Controls | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Estimated protection, % (95% CI) |
|---|---|---|---|---|---|
| *Reinfection defined as a new positive PCR test at least 90+ days after primary infection* | | | | | |
| | **BA.5 cases** | | | | **protection against BA.5** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 212 ( 2.4) | 20,387 (21.3) | 0.093 (0.081; 0.106) | 0.075 (0.065; 0.086) | 92.5 (91.4; 93.5) |
| **Unexposed** | 8,448 (97.6) | 75,292 (78.7) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 66 ( 0.8) | 1,930 ( 2.4) | 0.305 (0.238; 0.390) | 0.273 (0.212; 0.350) | 72.7 (65.0; 78.8) |
| **Unexposed** | 8,448 (99.2) | 75,292 (97.6) | 1 | 1 | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 59 ( 0.7) | 1,092 ( 1.4) | 0.482 (0.370; 0.626) | 0.388 (0.296; 0.507) | 61.2 (49.3; 70.4) |
| **Unexposed** | 8,448 (99.3) | 75,292 (98.6) | 1 | 1 | |
| | **BA.2 cases** | | | | **protection against BA.2** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 64 ( 0.8) | 20,387 (21.3) | 0.028 (0.022; 0.036) | 0.027 (0.021; 0.035) | 97.3 (96.5; 97.9) |
| **Unexposed** | 8,461 (99.2) | 75,292 (78.7) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 41 ( 0.5) | 1,930 ( 2.5) | 0.189 (0.139; 0.258) | 0.188 (0.138; 0.257) | 81.2 (74.3; 86.2) |
| **Unexposed** | 8,461 (99.5) | 75,292 (97.5) | 1 | | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 24 ( 0.3) | 1,092 ( 1.4) | 0.196 (0.130; 0.293) | 0.186 (0.124; 0.280) | 81.4 (72.0; 87.6) |
| **Unexposed** | 8,461 (99.7) | 75,292 (98.6) | 1 | 1 | |

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from May 10, 2022 to June 30, 2022; controls tested negative during the same period. OR denotes odds ratio; CI denotes confidence interval. Exposed individuals had a positive SARS-CoV-2 PCR test between January 1 and February 9, 2022. Unexposed individuals had no positive PCR tests before the start of follow-up on May 10, 2022. *adjusted for age group, time (week number), sex, region and comorbidity.

**Table s7** Sensitivity analysis with reinfection defined as a new positive PCR test any time after the primary infection: Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, April to June, 2022, Denmark.

| | Cases | Controls | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Estimated protection, % (95% CI) |
|---|---|---|---|---|---|
| *Reinfection defined as a new positive PCR test any time after primary infection* | | | | | |
| | **BA.5 cases** | | | | **protection against BA.5** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 332 ( 3.8) | 66,146 (31.4) | 0.086 (0.077; 0.096) | 0.056 (0.050; 0.062) | 94.4 (93.8; 95.0) |
| **Unexposed** | 8,468 (96.2) | 144,697 (68.6) | 1 | 1 | |
| | **BA.2 cases** | | | | **protection against BA.2** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 624 ( 2.1) | 66,146 (31.4) | 0.047 (0.043; 0.051) | 0.052 (0.048; 0.056) | 94.8 (94.4; 95.2) |
| **Unexposed** | 29,100 (97.9) | 144,697 (68.6) | 1 | 1 | |

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 30, 2022; controls tested negative during the same period. OR denotes odds ratio; CI denotes confidence interval. Exposed individuals had a positive SARS-CoV-2 PCR test between January 1 and April 9, 2022. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for age group, time (week number), sex, region and comorbidity.

**PROTECTION AGAINST REINFECTION: SENSITIVITY ANALYSIS 3**

**Table s8** Sensitivity analysis with additional adjustment for time since third vaccine dose: Protection against BA.5 and BA.2 infection after a prior positive SARS-CoV-2 PCR test, April to June, 2022, Denmark.

| | Cases | Controls | Unadjusted OR (95% CI) | Adjusted* OR (95% CI) | Estimated protection, % (95% CI) |
|---|---|---|---|---|---|
| | **BA.5 cases** | | | | **protection against BA.5** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 210 ( 2.4) | 33,972 (19.0) | 0.106 (0.092; 0.121) | 0.072 (0.063; 0.083) | 92.8 (91.7; 93.7) |
| **Unexposed** | 8,468 (97.6) | 144,697 (81.0) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 65 ( 0.8) | 3,336 ( 2.3) | 0.334 (0.261; 0.427) | 0.275 (0.213; 0.354) | 72.5 (64.6; 78.7) |
| **Unexposed** | 8,468 (99.2) | 144,697 (97.7) | 1 | 1 | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 58 ( 0.7) | 1,878 ( 1.3) | 0.528 (0.406; 0.686) | 0.413 (0.315; 0.542) | 58.7 (45.8; 68.5) |
| **Unexposed** | 8,468 (99.3) | 144,697 (98.7) | 1 | 1 | |
| | **BA.2 cases** | | | | **protection against BA.2** |
| *Exposure: prior omicron infection* | | | | | |
| **Exposed** | 192 ( 0.7) | 33,972 (19.0) | 0.028 (0.024; 0.032) | 0.029 (0.025; 0.034) | 97.1 (96.6; 97.5) |
| **Unexposed** | 29,100 (99.3) | 144,697 (81.0) | 1 | 1 | |
| *Exposure: prior delta infection* | | | | | |
| **Exposed** | 100 ( 0.3) | 3,336 ( 2.3) | 0.149 (0.122; 0.182) | 0.159 (0.130; 0.194) | 84.1 (80.6; 87.0) |
| **Unexposed** | 29,100 (99.7) | 144,697 (97.7) | 1 | | |
| *Exposure: prior alpha infection* | | | | | |
| **Exposed** | 98 ( 0.3) | 1,878 ( 1.3) | 0.259 (0.212; 0.318) | 0.270 (0.220; 0.332) | 73.0 (66.8; 78.0) |
| **Unexposed** | 29,100 (99.7) | 144,697 (98.7) | 1 | 1 | |

All participants had received 3 mRNA COVID-19 vaccine doses. Cases were infected with either BA5 or BA.2 during the outcome period from April 10, 2022 to June 30, 2022; controls tested negative during the same period. OR denotes odds ratio; CI denotes confidence interval. Unexposed individuals had no positive PCR tests before the start of follow-up on April 10, 2022. *adjusted for age group, time (week number), sex, region, comorbidity and time since third vaccine dose (categorical variable with six levels: 0-60 days, 61-90 days, 91-120 days, 121-150 days, 151-180 days, 181-210 days, 210+ days).

**VACCINE PROTECTION: SENSITIVITY ANALYSIS 1**

To restrict heterogeneity in the time since booster dose vaccination, only those who received their third dose in January 2022 are included in this sensitivity analysis (as well as those completely unvaccinated).

**Table s9** Sensitivity analysis including unvaccinated and those vaccinated with a third dose in January 2022 only: Vaccine protection against infection with BA.5 relative to BA.2, April to June, 2022, Denmark.

| | Type of infection contracted during outcome period | | | |
|---|---|---|---|---|
| **Exposure (vaccination status)[$]** | **Infected with BA.5** | **Infected with BA.2** | **Unadjusted OR (95% CI)** | **Adjusted* OR (95% CI)** |
| *Three doses versus unvaccinated* | | | | |
| **Three doses (3rd dose in Jan 22)** | 1,544 (73.0) | 4,210 (71.3) | 1.09 (0.97; 1.21) | 1.11 (0.91; 1.37) |
| **Unvaccinated** | 571 (27.0) | 1,691 (28.7) | 1 | 1 |
| *Three versus two doses* | | | | |
| **Three doses (3rd dose in Jan 22)** | 1,544 (75.1) | 4,210 (73.5) | 1.08 (0.97; 1.22) | 1.05 (0.85; 1.30) |
| **Two doses** | 513 (24.9) | 1,515 (26.5) | 1 | 1 |

All participants were infected with either BA.5 or BA.2. The outcome period was between April 10, 2022 and June 30, 2022. The analysis includes both those with and without a previous infection before April 10, 2022. OR denotes odds ratio; CI denotes confidence interval. *Adjusted for age group, time (week number), sex, region, comorbidity and prior infection (yes/no). $ Three doses: 3 doses of mRNA-1273 or BNT162b2 before March 27, 2022; two doses: completed primary vaccination series >140 days before the outcome period.